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PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

Dihydroorotic and Salts

We, ED. GEISTLICH SOHNE A.G., a Swiss Body Corporate, of Wolhusen, Lucerne, Switzerland, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to novel chemical compounds of use in geriatry.

Orotic acid, uracil-4-carboxylic acid, was isolated from milk for the first time in 1904 and has been found to be of importance in purine metabolism. In fact in both the young and the aging organism orotic acid plays a central role in protein and purine metabolism and is thus employed in geriatry both as the free acid and also as salts such as magnesium orotate.

It exerts a liver-protecting activity by formation of nucleic acids in the liver cells which may be detected by normal protein synthesis. Orotic acid also possesses a useful cholesterol-lowering activity, reducing the deposition of lipoids in the coronary artery, the aorta and other blood vessels. It has also been found that dihydroorotic acid possesses similar properties.

We have now found that aliphatic amines carrying a hydrophilic group such as a hydroxyl or amide group form salts with dihydroorotic acid which possess several advantages over the free acid or its metal salts.

These salts are surprisingly stable and without difficulty form 10-20% aqueous solutions whereas free dihydroorotic acid is substantially insoluble in cold water and the metal salts only sparingly soluble. Aqueous solution of the salts of the present invention of up to 50% have, in fact, been prepared.

Further, the new salts show very low toxicity and a good physiological compatibility, particularly compatibility in the stomach. In our investigations, they have shown a relatively constant blood-level and an improved diffusion ratio and improved the capillary blood flow and generally promoted an easier flow of blood through the vascular system. The new salts have also been found to produce improvements in depth of sleep, in the level of depression and exhaustion and general condition and alertness.

According to the present invention therefore we provided salts of dihydroorotic acid with primary, secondary or tertiary aliphatic amines, said amines having in the molecule at least one other hydrophilic group as defined hereinafter.

The term 'aliphatic amine' as used herein refers to amines in which an aliphatic group is directly bonded to a substituted or unsubstituted amino group; the aliphatic grouping may carry, besides the specified hydrophilic groups, other groups such as aryl groups.

Suitable hydrophilic groups according to the present invention comprise hydroxy; esterified hydroxy e.g. *p*-amino-benzoxy; carboxy; amino and carbamoyl groups. Where two or more hydrophilic groups are present in the molecule they may be the same or different.

Preferred amines for salt-formation according to the present invention are aminoethanol and mono- and di-alkylaminoethanols, particularly methylaminoethanol ethylaminoethanol, dimethylaminoethanol, diethylaminoethanol and methylethylaminoethanol.

Other useful amines include β-diethylaminobutyranilide and procaine.

Particularly preferred salts according to the present invention are the aminoethanol salts of dihydroorotic acid, especially dimethylaminothanol dihydroorotate. These in particular show very low toxicity, the LD_{50}

of dimethylaminoethanol dihydroorotate in rats and mice being over 5000 mg/kg.

According to a further feature of the present invention we provide a process for the preparation of the new salts according to the invention comprising reacting dihydroorotic acid or a salt thereof with a primary, secondary or tertiary aliphatic amine carrying at least one further hydrophilic group as defined above or a salt thereof whereby the amine dihydroorotate is formed.

Preferably the acid and amine are heated together with or without an added solvent. The molar ratio may conveniently be 1 : 1 or an excess of the amine may be used. The added solvent may, for example, be water or an organic solvent such as an alkanol e.g. methanol, ethanol or isopropanol; an ester e.g. ethyl acetate or amyl acetate; a cyclic ether e.g. dioxan or tetrahydrofuran, or a substituted amide e.g. dimethylformamide or dimethylacetamide. The crystalline salt may then be isolated, for example, by concentration of the reaction mixture, e.g. under vacuum.

According to a further feature of the present invention, we provide pharmaceutical compositions comprising, as active ingredient, at least one of the compounds according to the invention in association with a pharmaceutical carrier or excipient. The compositions may be presented in a form suitable for oral, rectal, topical or parental administration. Thus, for example, compositions for oral administration may be solid or liquid and may take the form of granules, tablets, coated tablets, effervescent tablets, capsules, syrups, emulsions, suspensions or drops, such compositions comprising carriers or excipients conventionally used in the pharmaceutical art. Thus, for example, suitable tabletting excipients include lactose, potato and soluble starches and magnesium stearate.

For parenteral administration, the carrier may be a sterile, parenterally acceptable liquid such as sterile water, or a parenterally acceptable oil, e.g. arachis oil, contained in ampoules. Compositions for rectal administration may take the form of suppositories, the carrier comprising a suppository base.

Compositions for topical application may, for example, take the form of creams, ointments or lotions.

Advantageously, the compositions may be formulated as dosage units, each unit being adapted to supply a fixed dose of active ingredient. Tablets, coated, tablets, effervescent tablets, capsules, suppositories and ampoules are examples of suitable dosage unit forms. Each dosage unit preferably contains 10.0 to 200.0 mg, and advantageously 20.0 to 50.0 mg of active ingredient especially 25 mg.

The compositions according to the present invention may further contain other useful physiologically active ingredients for example, vitamins, minerals, amino acids or enzymes.

Vitamins can be added readily to creams, especially creams consisting of water-oil emulsions. Vitamins A.D.E. and K. are soluble in the oil phase while vitamins B_1, B_2, B_8, B_{12} and C are soluble in the aqueous phase. The dialkylaminoethanol dihydroorotates can well be added to the cream in the aqueous phase.

The dihydroorotate salts are absorbed from the skin and cause increased circulation of the blood. This effect is increased by addition of vitamins and enzymes or enzyme systems such as phosphatases, which influence the cell respiration favourably. Particularly useful materials containing enzymes are placenta-extracts from cows, sheep and pigs and also human placenta extracts. These should be extracted at the lowest temperature possible (not about 40°C). At this temperature, the natural enzyme system will not be destroyed.

Such creams successfully influence symptoms of age appearing on the surface area of the body. The skin becomes smoother, shrinking of the skin due to water losses is checked and the metabolic products in the form of pigments on the skin are at least partly eliminated. Also, deep-seated spasms and muscle pains of the rheumatic type are favourably influenced by creams of this type.

The preferred concentration of the active dihydroorotate in such topical formulations is 0.01 to 1% by weight preferably about 0.1%.

The following examples illustrate the preparation of compounds according to the invention, and also pharmaceutical compositions containing such compounds as active ingredients:—

Example 1

2-Diethylaminoethanol-dihydroorotate

0.79 g of dihydroorotic acid were suspended in 30 ml. of ethanol and 0.67 ml. of diethylaminoethanol were added. The mixture was heated at 70°C until the dihydroorotic acid formed a clear solution. The reaction mixture was filtered hot and evaporated to dryness *in vacuo* at 30-40°C.

Yield: 1.4 g of dihydroorotate; readily soluble in water.

Found: C, 48.01 H, 8.00 N, 15.52%

$C_{11}H_{21}N_3O_5$ (275.30) requires: C, 47.99 H, 7.69 N, 15.27%

Example 2

β-Diethylaminobutyranilide dihydroorotate

0.79 g. of dihydroorotic acid was suspended in 30 ml of ethanol and 1.17 g. of β-diethylaminobutyranilide. The reaction mixture was then heated to 70°C until a clear solution was formed. This warm solution was filtered and concentrated to dryness *in vacuo* at 40°C.

Yield: 1.9 g of dihydroorotate; readily soluble in water.
Found: C, 58.90 H, 7.58 N, 13,82%
$C_{19}H_{28}N_4O_5$ (392.45) requires: C, 58.14 H, 7.19 N, 14.28%

Example 3
Procaine dihydroorotate

0.79 g. of dihydroorotic acid were suspended in 30 ml of ethanol and 1.18 g. of procaine base added. The whole was refluxed for 20 minutes until a clear solution was formed. This hot solution was filtered and evaporated to dryness *in vacuo*.

Yield: 1.8 g. of dihydroorotate; readily soluble in water.
Found: C, 54.84 H, 6.68 N, 14.36%
$C_{18}H_{26}N_4O_6$ (394.42) requires: C, 54.81 H, 6.64 N, 14.21%

Example 4
Dimethylaminoethanol dihydroorotate

1.58 g. dihydroorotic acid were suspended in 50 ml ethanol and 1 ml dimethylaminoethanol was added. The reaction mixture was then heated at 70°C for 5-10 minutes to yield a clear solution. After filtration the alcoholic solution was evaporated to dryness under reduced pressure at not more than 40°C to yield the desired dihydroorotate. (Yield: 2.3 g.). The product is readily soluble in water, and is hygroscopic; taking up one molecule of water of crystallisation.

Melting point (120°C) 150-160°C (decomposition)
Found: C, 43.70 H, 6.96 N, 17.06%
$C_9H_7N_3O_5$ (247.23) requires: C, 43.72 H, 6.93 N, 17.00%
Found: C, 41.13 H, 6.88 N, 15.84%
$C_9H_{17}N_3O_5 \cdot H_2O$ requires: C, 40.89 N, 7.18 N, 15.82%

Example 5 Capsules

Each capsule contains:

dimethylamino-ethanol dihydroorotate	25 mg
vitamin A	10,000 i.u.
vitamin B_1	10 mg
vitamin B_2	3 mg
vitamin B_6	5 mg
vitamin B_{12}	5 mcg
nicotinamide	10 mg
Panthenol	10 mg
vitamin C	70 mg
vitamin D_3	400 i.u.
vitamin E	15 mg
calcium (as monohydrogen phosphate	25 mg
magnesium (as orotate)	7 mg
iron (as fumarate)	6.5 mg
manganese as sulphate)	0.5 mg
phosphorus (as calcium monohydrogen phosphate)	19 mg
copper (as sulphate)	1 mg
zinc (as sulphate)	1 mg
calcium magnesium inositol hexaphosphate	50 mg
rutine	10 mg
adenosine	1 mg
choline bitartrate	50 mg

The ingredients are mixed together and filled into capsule shells.

Example 6 Effervescent tablets.

Each tablet contains:

dimethylaminoethanol dihydroorotate	25 mg
vitamin A	10,000 i.u.
vitamin B_1	10 mg
vitamin B_2	3 mg
vitamin B_6	5 mg
vitamin B_{12}	5 mcg
nicotinamide	10 mg
calcium pantothenate	10 mg
vitamin C	70 mg
vitamin D_3	400 i.u.
vitamin E	15 mg
calcium (as glycerophosphate)	19 mg
magnesium (as orotate)	7 mg
iron (as carbonate saccharate)	2 mg
manganese (as sulphate)	0.5 mg
phosphorus (as calcium glycerophosphate)	15 mg
copper (as sulphate)	1 mg
zinc (as sulphate)	1 mg
calcium magnesium inositol hexaphosphate	50 mg
rutine	10 mg
adenosine	50 mg
choline bitartriate	50 mg

The ingredients are mixed with an effervescent tablet base and pressed into tablets.

Example 7 Cream containing 0.1% dimethylaminoethanol dihydroorotate.

Component A)	100.0 g	Hide fat
	120.0 g	Gezetan E*
	40.0 g	Lanolin B.P.
	1.5 g	Propyl p-Hydroxybenzoate B.P.
Component B)	489.0 g	Water
	50.0 g	Glycerine
	2.0 g	Sorbic acid
	1.0 g	Dimethylaminoethanol dihydroorotate
Component C)	200.0 g	Oil-soluble placenta extract

Component A is heated to melting on the water bath, cooled to 40°C and warmed with stirring still at 40°C with Component B. The temperature should not be allowed to exceed 40°C. Component C is then added, stirred until cool and finally triturated 3 times in a roll mill.

* Non-ionic wax-like oil-in-water type emulsifying agent with added saturated fatty alcohol.

WHAT WE CLAIM IS:—

1. Salts of dihydroorotic acid with primary, secondary or tertiary aliphatic amines, said amines having at least one other hydrophilic group in the molecule, said hydrophilic groups comprising hydroxy, esterified hydroxy, carboxy, amino or carbamoyl groups.

2. Compounds as claimed in claim 1 in which the amines are amino-ethanol and mono- and dialkylaminoethanols.

3. Compounds as claimed in claim 2 in which the amines are methylaminoethanol, ethylaminoethanol, dimethylaminoethanol, diethylaminoethanol and methylethylaminoethanol.

4. Dimethylaminoethanol dihydroorotate.

5. Diethylaminoethanol dihydroorotate.

6. Salts of dihydroorotic acid specifically as herein described, other than dimethylaminoethanol dihydroorotate and diethylaminoethanol dihydroorotate.

7. A process for the preparation of compounds as claimed in claim 1, comprising reacting dihydroorotic acid, or a salt thereof, with a primary, secondary or tertiary aliphatic amine carrying at least one further hydrophilic group as defined in claim 1, or a salt thereof whereby the amine dihydroorotate is formed.

8. A process as claimed in claim 7 in which the acid and amine are heated together.

9. A process as claimed in claim 8 in which the reaction is effected in an added solvent.

10. A process as claimed in claim 9 in which the solvent is water or an alkanol, an ester, a cylic ether or a substituted amide.

11. A process as claimed in claim 10 in which the solvent is methanol, ethanol, isopropanol, ethyl acetate, amyl acetate, dioxan, tetrahydrofuran, dimethylformamide or dimethylacetamide.

12. A process as claimed in any of claims 7 to 11 in which the molar ratio of amine to acid is 1 : 1, or an excess of the amine is used.

13. A process as claimed in claim 7 substantially as herein described.

14. A process as claimed in claim 7 substantially as herein described in any of Examples 1 to 15.

15. Pharmaceutical compositions comprising at least one compound as claimed in claim 1 in association with a pharmaceutical carrier or excipient.

16. Compositions as claimed in claim 15 in a form suitable for oral, rectal, topical or parenteral administration.

17. Compositions as claimed in claim 16 in the form of granules, tablets, coated tablets, effervescent tablets, capsules, syrups, emulsions, suspensions, drops, ampoules, creams, lotions, ointments or suppositories.

18. Compositions as claimed in claim 15 in the form of dosage units.

19. Compositions as claimed in claim 18 containing 10 to 200 mg of active ingredient per dosage unit.

20. Compositions as claimed in claim 18 containing 20 to 50 mg of active ingredient per dosage unit.

21. Compositions as claimed in any of claims 15 to 20 further containing other useful physiologically active ingredients.

22. Compositions as claimed in claim 21 in which the further ingredients are vitamins, minerals, amino acids or enzymes.

23. Compositions as claimed in claim 15 substantially as herein described.

24. Compositions as claimed in claim 15 substantially as herein described in Example 16 or Example 17.

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